

13
B3
contd

hardening at body temperature.

B4
2nd
AS

26. (Twice amended) A method for stimulating an immune response in a mammal, said method comprising:

administering to the mammal an injectable paste comprised of a hardenable calcium phosphate composition, wherein the paste hardens at body temperature and stimulates an immune response in the host.

27. (Twice amended) A method for increasing the immunogenicity of an antigen in a mammal, said method comprising:

co-administering both the antigen and a composition comprising a calcium phosphate paste capable of hardening at body temperature.

Remarks

I. The Office Action.

Claims 1-3, 5-6, 7-31 and 33-44 are pending in the above-identified application. Claims 1, 5, 13, 14, 15, 26, and 27, are amended. Claims 1, 13-15, and 38-44 stand rejected under 35 U.S.C. §112, first paragraph; and claims 1-3, 5-6, 7-31 and 33-44 stand rejected under 35 U.S.C. §103(a). Reconsideration of the claims is requested.

II. Applicant's Invention.

The invention is directed to immunological adjuvant composition useful for enhancing the immune response against antigens. The adjuvant composition includes a

first adjuvant including amorphous calcium phosphate (ACP) formulated as an injectable paste having a solids content of greater than 40 wt %.

The adjuvant composition alternatively includes a first adjuvant as an injectable calcium phosphate composition that is capable of hardening at body temperature. The injectability and hardening ability of the adjuvant improves adjuvant and antigen delivery.

The adjuvant composition alternatively includes a first adjuvant including calcium phosphate, and a second adjuvant, wherein the first and second adjuvant are selected to elicit a immunological response of a specific immune cell-type. The use of a second adjuvant augments the effect observed in the primary adjuvant, either by enhancing a response in the same cell type or eliciting an immune response in a different cell type.

III. The Cited References.

Towey describes a calcium phosphate gel, which may be used as an adjuvant in the production of immunizing agents (col. 3, l. 54-56). The gel can contain as much as 15% solids, but is usually much more dilute (col. 3, l. 15-16). Towey teaches administration of the calcium phosphate as a dilute gel or in tablet form (col. 4, l. 19-23). The low solids content gels of Towey are inherently incapable of hardening.

The calcium phosphate gels of Gupta described in Table IV have solid contents of about 0.2%, i.e., about 0.002 g calcium and phosphorous in 1 mL (1 g) of liquid.¹ There

¹ This calculation does not take into account the presence of other atoms in the solid, e.g., oxygen and/or hydrogen; however, it is unlikely that the total solids content exceeds 1%.

is no teaching of using amorphous calcium phosphate formulated as an injectable paste having a solids content of greater than 40 wt%. The low solids content gels of Gupta are inherently incapable of hardening.

Lee et al. teaches a reactive calcium phosphate paste including an amorphous calcium phosphate and a second calcium phosphate that hardens at room and body temperatures. There is no teaching or suggestion that the paste is suitable for use in an adjuvant composition or for enhancing an immune response against antigens.

IV. Rejection of the claims under 35 U.S.C. § 112, first paragraph.

Claims 1, 13-15 and 38-44 stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner does not consider the terms “an injectable paste having a solids content of greater than 40 wt%” and “self-setting” to be supported in the original specification.

To satisfy the written description requirement, the application as filed “must . . . convey with reasonable clarity to those skilled in the art that . . . [the inventor] was in possession of the invention.” *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The original disclosure need not provide word-for-word support for the claimed subject matter at issue. *See In re Wright*, 866 F.2d 422, 425, 9 USPQ2d 1649, 1651 (Fed. Cir. 1989). Rather, one skilled in the art, reading the

original disclosure, must “immediately discern the limitation at issue” in the claims.

Waldemar Link GmbH & Co. v. Osteonics Corp., 32 F.3d 556, 558, 31 USPQ2d 1855, 1857 (Fed. Cir. 1994).

The specification describes hydrated precursors containing amorphous calcium phosphate prepared using 0.7-1.5 ml H₂O (density = 1 g/mL) per 1 gram of mixed powder (page 52, lines 1-2). Thus, at one end of the range 1 gram of a 1.7 gram paste is solids (59% solids); and at the other endpoint, 1 gram of a 2.5 gram paste is solids (40% solids). Other examples show 1:1 liquid:solid paste (50% solids) (p. 15, l. 12), and 0.8:1 liquid:solid paste (44% solids) (p. 62, l. 7-8).

Having demonstrated solid contents of 40 wt%, 44 wt%, 50 wt%, and 59 wt%, Applicants are entitled to claim a solids content of “greater than 40%”. Even though the precise range of the claim (“greater than or equal to 40 wt%”) is not repeated verbatim in the specification, one skilled in the art would understand that the paste contains at least 40 wt% solids, but that the upper limit is set by the requirement that the paste remain injectable. Accordingly, the claim limitation of “a solids content of greater than or equal to 40 wt%” is adequately described by the specification, and the rejection of claim 33 under 35 U.S.C. § 112, ¶ 1, may be withdrawn.

The term “self-setting” is canceled from the claims, thereby obviating the rejection.

V. Rejection of the claims under 35 U.S.C. § 103(a).

Claims 1-3, 5-6, 7-31 and 33-44 stand rejected under 35 U.S.C. §103(a) as being

unpatentable over Towey and Gupta in view of Lee et al. (USP 5,676,976).

Claims 1-2, 6-7, 13-14, 26-27, 34 and 37 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Towey et al.

Claims 1-2, 6, 10-11, 13-15, 19, 23-24, 26-30, 34-35, and 37 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Gupta.

Obviousness may be established from a single prior art reference or a combination of prior art references; however, there must be a showing of a suggestion or motivation to modify or combine the teachings of the references in order to support the obviousness conclusion. This suggestion or motivation may be derived from the prior art references themselves, from the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved.

(A) Rejection of claims directed to amorphous calcium phosphate adjuvant.

Claims 1, 13, and 14 are directed to an adjuvant composition (or its use) comprising amorphous calcium phosphate, which is formulated as a *paste* having at least a 40 wt% solids content.

Gupta and Towey both teach calcium phosphate *gels* as an adjuvant composition. Towey discloses gels having a calcium phosphate solids content of up to 15 wt%, but teaches much lower solids content when used as an adjuvant (col. 3, l. 65-70). Gupta describes gels having a solids content on the order of 1 wt%. The examiner suggests that one skilled in the art would have been motivated to optimize the workable range of solid

content in their adjuvant composition by routine experimentation. Applicants respectfully disagree.

The high solids content of the instantly claimed adjuvant *paste* provides a fundamentally different adjuvant composition than the low solids content calcium phosphate *gels* of the prior art. There is no suggestion in the prior art that optimization of a gel-based vaccine includes increasing the solids content of the calcium phosphate.

A gel is a colloidal suspension of a liquid in a solid, so that the material contains fluid-filled interstices and has a very high surface area. A gel provides entrained liquid domains in which antigens may be located in addition to providing large surface area for adsorbing antigen. Antigen is released by desorption of the sorbed material and/or its free diffusion in the liquid phase.

A paste, on the other hand, is a mixture of particles with sufficient fluid to wet the particle surfaces. A paste also provides an adsorptive surface, and, if hardened, a rigid matrix for release. Access to the paste interior is significantly hindered, thereby fundamentally changing the nature of antigen presentation to the host. Release of the antigen from the calcium phosphate paste is a function of many factors, such as its porosity and degradability. Thus, the claimed paste formulation of the calcium phosphate adjuvant provides a substantially different environment for stimulating an immune response than the gels of the prior art.

There is not a hint of a suggestion in either of Towey or Gupta to increase the solids content of the calcium phosphate adjuvant or to substitute a *paste* for a *gel* in the

adjuvant formulation. To suggest that drastically increasing the solids content of the adjuvant amounts to mere routine optimization of the solids content of the composition runs counter to conventional wisdom and established protocol in the vaccine art. The degree of antigen adsorption onto aluminum and calcium phosphate gels or suspensions markedly affects adjuvancy. See, Gupta *et al.* Calcium phosphate adjuvants have been overwhelmingly and exclusively employed in gel form prior to discovery by the Applicants that calcium phosphate pastes may function as adjuvants. Gupta *et al.*; and see also, newly cited Kato *et al.*, *Microbiol. Immunol.* **38**(7):543 (1994); E.H. Relyveld, *Dev. Biol. Stand.* **65**:131 (1986); Goto *et al.*, *Vaccine* **11**(a):914 (1993); Gupta *et al.*, *Vaccine* **11**(3):293 (1993); and Goto *et al.*, *Vaccine* **15**(12-13):1364 (Aug-Sept 1997). In view of the strong teaching in the vaccine art that a low solids content gel with large surface area for antigen adsorption is the adjuvant of choice, the Examiner's assertion that the pastes of the instant invention represent an obvious optimization of the workable range of the adjuvant composition is not sustainable. Thus, one would not be motivated to look to pastes as optimized adjuvants absent an express suggestion in the prior art. Since neither Gupta nor Towey provide the requisite suggestion, the instant claims are patentable over these references.

Lee does not remedy the deficiencies of Towey and Gupta. The fact that Lee discloses an amorphous calcium phosphate paste in a pharmaceutical formulation does not provide adequate suggestion or motivation to use such materials in a vaccine composition. Lee is primarily concerned with use of a self-hardening calcium phosphate

material in bone-related applications and with the suitability of the material as a bone substitute. The Examiner considers Lee to be particularly relevant because Lee discloses the addition of proteins or polypeptides in the calcium phosphate paste (page 9, paragraph 9). In fact, Lee discloses only the addition of bone regenerative proteins.

The inclusion of bone regenerative proteins in Lee's calcium phosphate paste gives no indication of the paste's effectiveness in a vaccine formulation. Adjuvants have significantly different performance objectives than bone defect healing materials, e.g., enhancing host immune response vs. remodeling damaged bone. It is not at all obvious that a material used in the treatment of bone disease should or could be successfully used as a vaccine adjuvant. Nor is the incorporation of bone regenerative protein into the paste relevant or suggestive of the incorporation of proteins related to cellular or molecular immunity into the composition. For example, successful delivery of an antigen includes preservation of the antigen's conformational properties, whereas conformational changes may be better tolerated in other applications. The addition of one class of peptides into a composition does not suggest the incorporation of a different class with completely different functionality.

In summary, the mere existence of a calcium phosphate paste that has been successfully used in treatment of bone disorders does not suggests its use in other unrelated, and untested, applications. There is simply no motivation to use the calcium phosphate pastes of Lee in the calcium phosphate adjuvants of Towey or Gupta.

For the foregoing reasons, it is submitted that there is no teaching or suggestion in

the cited art for the invention as set forth in claims 1, 13, and 14, and those claims dependent thereon.

(B) Rejection of claims directed to a hardenable calcium phosphate composition.

Claims 15, 26 and 27 are directed to an adjuvant composition (or its use) comprising a hardenable calcium phosphate composition. The adjuvant composition may be formed as an injectable paste and hardened *in vivo*. The hardening ability of the adjuvant provides for a depot that retains its physical integrity *in vivo* and extends adjuvant delivery time.

There is no appreciation of any of these features in the adjuvant compositions Gupta and Towey. These compositions are inherently incapable of hardening due to their high liquid contents, and there is no suggestion that the ability to harden is a desired attribute in a vaccine adjuvant. While Lee teaches a hardenable calcium phosphate composition, there is no teaching or suggestion that the paste is suitable for use in an adjuvant composition or for enhancing an immune response. As stated above, the incorporation of peptides into the calcium phosphate composition for bone repair does not suggest the incorporation of immunogenic or antigenic peptides of the invention or the use of the composition as an adjuvant.

In summary, the requisite suggestion to combine the references, which must be found in the prior art and not in Applicants' invention, is missing.

For the foregoing reasons, it is submitted that there is no teaching or suggestion in

the cited art for the invention as set forth in claim 15, 26 or 27, and those claims dependent thereon.

(C) Rejection of claims directed to a two-adjuvant composition.

Claims 28 and 37 are directed to an adjuvant composition (or its use) comprising a first calcium phosphate adjuvant and a second adjuvant, wherein the first and second adjuvant are selected to elicit a immunological response of a specific immune cell-type. The examiner refers to Gupta for teaching that aluminum compounds have been used with other non-calcium phosphate adjuvants, and asserts that it would have been obvious to combine a calcium phosphate adjuvant with additional adjuvants.

Gupta does not provide any guidance as to the selection of the second adjuvant, and a fair reading of Gupta would suggest that there is no particular preference of a second adjuvant. In contrast, the instantly claimed invention requires selection of the second adjuvant such that an immunological response of a specific cell type is elicited. This reflects the appreciation that calcium phosphates are capable of eliciting a response from specific cell types. This recognition is first shown in Example 18 of the instant application.

As is recognized in Gupta, calcium phosphate is more biologically compatible than aluminum compounds. While this may make calcium phosphate an attractive alternative adjuvant to aluminum compounds, it also may have the undesired effect of providing a more muted immunological response. For the first time, the present invention recognizes

that such subtleties in performance may be exploited by combining two adjuvants to elicit specific immunological responses.

For the foregoing reasons, it is submitted that claims 1-3, 5-6, 7-31 and 33-44 are patentable over the cited art. A favorable notice to that effect is requested.

VI. Miscellaneous.

Enclosed is a petition to extend the period for replying for three months, to and including March 12, 2001. Also enclosed is a to cover the fees set forth in 37 C.F.R. § 1.17(a)(3). If there are any additional charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date:

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Mary Rose Scozzafava
Mary Rose Scozzafava
Reg. No. 36,268

Clark & Elbing LLP
176 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045



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PATENT TRADEMARK OFFICE



**Marked-up claims showing all changes
relevant to the previous versions of the claims**

1. (Twice Amended) An immunological adjuvant composition useful for enhancing the immune response against antigens, comprising:

a first adjuvant, where said first adjuvant comprises amorphous calcium phosphate formulated as an injectable paste having a solids content of greater than or equal to 40 wt%.

5. (Once Amended) A composition of claim 3[4], wherein 25-100% by weight of said composition consists of said particles having a diameter between 0.1 nm and 900 nm.

13. (Twice Amended) A method for stimulating an immune response in a mammal, said method comprising:

administering to the mammal a composition comprising amorphous calcium phosphate formulated as an injectable paste having a solids content of greater than or equal to 40 wt%.

14. (Twice Amended) A method for increasing the immunogenicity of an antigen in a mammal, said method comprising:

co-administering both an antigen and a composition comprising amorphous calcium phosphate formulated as an injectable paste having a solids content of greater than or equal to 40 wt %.

15. (Twice Amended) An immunological adjuvant composition useful for enhancing the immune response against antigens, comprising:

a first adjuvant[, where said first adjuvant comprises a self-setting, hardenable] comprised of an injectable calcium phosphate paste capable of hardening at body temperature [composition].

26. (Twice Amended) A method for stimulating an immune response in a mammal, said method comprising:

administering to the mammal [a composition] an injectable paste comprised of [comprising] a [self-setting,] hardenable calcium phosphate composition, wherein the paste hardens at body temperature and stimulates an immune response in the host.

27. (Twice Amended) A method for increasing the immunogenicity of an antigen in a mammal, said method comprising:

co-administering both the antigen and a composition comprising a [self-setting, hardenable] calcium phosphate [composition] paste capable of hardening at body temperature.